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Effects of hemodialysis and hypertonic hemodiafiltration on cardiac function compared

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Effects of hemodialysis and hypertonic hemodiafiltration on cardiac function compared. This study compared the acute and chronic effects on cardiac function of treatment with hypertonic hemodiafiltration (H HDF) and hemodialysis (HD). Cardiac function was assessed before, during and after a run of H HDF and HD using echocardiography and impedance cardiography in 10 patients in a randomized cross–over sequence, two months after stabilization on each treatment. Blood biochemistry was performed before and after each run. Ejection fraction and fractional shortening were significantly higher before the H HDF run, compared to the HD run, and this difference persisted during and after the treatment runs (both $P < 0.05$). There was a corresponding significant difference in the increase of the velocity of circumferential fiber shortening and in the reduction of end systolic diameter during and after H HDF ($P < 0.05$). Heart rate, stroke volume, cardiac output, systemic vascular resistance and mean arterial pressure did not differ significantly between the two treatments. Plasma calcium and bicarbonate were significantly higher ($P < 0.03$) at the start of H HDF and this difference was enhanced at the end of the run. In conclusion, H HDF compared with HD, is associated with a better myocardial function in both the short and long term treatments. The evidence suggests that this may be due to improved levels of plasma calcium, bicarbonate, and/or the removal of an as yet unidentified myocardial toxin.

Although hemodialysis (HD) is the standard method of solute removal in patients with chronic uremia, the frequent occurrence of side affects such as hypotension has prompted research into alternative methods of management. One such method is hemodiafiltration (HDF) which is capable of achieving an efficient removal of water and small and middle molecules from the blood [1]. Recently this technique has been modified to include simultaneous infusion of a hypertonic solution which is referred to as hypertonic hemodiafiltration (H HDF) [2, 3]. Clinical observations on patients undergoing this form of treatment suggest that they experience an enhanced sense of well-being and an improvement in dialysis tolerance (4).

The reasons for this improvement remain undefined and may be due to improvements in one or more of the many pathophysiological features associated with uremia, such as abnormalities of the cardiovascular and nervous systems. A number of non-invasive studies, using echocardiography, have examined the effects of HD on cardiac function [5, 6]. It has been shown that in patients with abnormal pre-dialysis end diastolic volume, a reduction in blood volume after HD resulted in a significant reduction in the stroke volume, end diastolic volume and left ventricular ejection time [5]. The end systolic volume was decreased also, but this change was not significant. Another report, however, indicated that the effects of regular HD can lead to improved cardiac function due to a combination of a decrease in end diastolic volume and an increase in left ventricular contractility [6]. There are no studies on the effects of H HDF on cardiac function.

A randomized cross–over study was done to examine the effects of HD and H HDF on cardiac function. Cardiac function was assessed in terms of changes in stroke volume, cardiac output, ventricular diameters, ejection time, mean velocity of fiber shortening, ejection fraction and fractional shortening of the left ventricle. Cardiac function was studied before, during and after a treatment run.

Methods

Patients

Thirteen, stable uremic patients at the Incentre Hemodialysis Unit of the University of Alberta Hospitals volunteered for a cross–over study which included four months each of HD and of H HDF in a random sequence. The study had been approved by the Ethical Review Committee of the University of Alberta Hospitals.

The criteria for admission to the study were: maintenance HD for at least six months previously, absence of other systemic diseases and no clinical evidence of coronary heart disease, heart failure or pericardial effusion.

The study protocol was completed by 10 out of the 13 patients. Of the drop–outs, one patient underwent kidney transplantation soon after commencing the study, the second declined to undergo the cardiac studies and the third dropped out during his HD control period for personal reasons.

The 10 patients (nine males, one female, mean age 36.5 ± 2.9 SEM years) were on various outpatient medications which were not changed throughout the study period. One patient had been prescribed a beta–blocker and another a vasodilator. None were taking digitalis.

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Table 1. Factors relating to dialysis treatments

Factor	Standard hemodialysis (N = 10)	P	Hypertonic hemodiafiltration (N = 10)
Pre-treatment body weight *kg*	76.5 ± 7.0		76.1 ± 6.8
Body weight loss achieved *kg*	2.8 ± 0.5	NS	2.9 ± 0.5
Duration of treatment *min*	240 ± 0	<0.01	204 ± 10
Weight loss rate *g/min*	11.5 ± 2.0	<0.01	14.5 ± 2.1
Blood flow rate *ml/min*	~250		~400
Dialysate flow rate *ml/min*	~500		~500
Dializer membrane and surface	Cuprophane or Cellulose Acetate (1.1–1.4 m^2)		Polyacrylonitrile (1.2 m^2)
Dialysis solution components *mmol/liter*			
Sodium	135.0		135.0
Potassium	1.0		1.0
Calcium	1.55		2.0
Magnesium	0.75		0.75
Chloride	105.6		111.5
Glucose	—		11.1
Acetate	35.0		30.0
Bicarbonate	35.0 (1 patient)		—
Acetic Acid	2.0 (1 patient)		—
Reinfusion solution components *mmol/liter*			
Sodium	—		180 or 220
Chloride	—		100 or 120
Bicarbonate	—		80 or 100

Means ± SEM — Student's paired t test.

Treatment methodology

The HD prescription was that deemed appropriate by the attending nephrologist at each session: the blood flow rate was ~250 ml/min; the sodium and the acetate concentration in the dialysate were 135 and 35 mmol/liter, respectively. One patient underwent bicarbonate dialysis. Hollow fiber dialyzers (cuprophane in 9, cellulose acetate in 1), with surface areas ranging from 1.1 to 1.4 m^2 (mean surface area 1.23 m^2) were used.

H HDF consists of a short time, low volume hemofiltration session (up to a maximum of six liters of postdilution replacing solution containing sodium at a concentration either of 180 or 220 mmol/liter) run concurrently with acetate HD (Na concentration in the dialysate 135 mmol/liter). The sodium modelling of H HDF has been described elsewhere [4, 7].

The equipment consisted of a dialysate delivery module in which a periodically renewed, fresh dialysate circulated in a predetermined constant volume. Any quantity of liquid removed from this closed circuit, that is, fixed volume, would be compensated automatically by an equal quantity of fluid extracted from the patient (Monitral, Hospal, Canada) [8]. The hypertonic solution was infused in a postdilution site with the aid of a roller pump (BSM 22, Hospal), the infusion rate of which could be manually regulated according to the requirements of fluid balance. The dialyzer used was the Biospal 3000 S (polyacrylonitrile membrane S, 1.2 m^2, Hospal).

Patients maintained their usual treatment schedule (three times a week) throughout the study. However, the treatment time was reduced during H HDF by 25 to 30 percent for all, as it had been previously demonstrated that this reduction in treatment time could be safely achieved [9]. The characteristics of the treatment modalities are shown in Table 1.

Three points are emphasized. First, a different blood flow rate and treatment time was maintained for the HD and H HDF runs in accordance with our routine practice. Second, for each patient the loss in body weight was matched and third, all the dialyses were performed with the same machine (Monitral, Hospal).

Assessment of cardiac function

Echocardiography. M-mode and two dimensional echocardiograms were obtained using a Diasonic CV60 Echocardiograph (Diasonics Inc., USA) with the patient in a supine, slightly left lateral position with the head and thorax elevated at 30° The phased array transducer (2.25 MHz) was positioned in the left parasternal position at the 3rd, 4th or 5th intercostal space to clearly visualize the left ventricle, first along the long axis view and then rotated 90° to the short axis view. Echocardiograms were simultaneously recorded with the electrocardiogram (lead II) on dry silver paper using a strip chart system (Model 4633A recorder, Tektronix, USA) at 50 mm/sec and on a videocassette using a videocassette recorder (Model BR6400U, JVC, Tokyo, Japan) recording M-mode and two dimensional echocardiograms, respectively. The transducer was maintained in the same position and angulation during the run in any one patient.

The two dimensional echocardiogram obtained allowed visualization of the left ventricular structures and accurate measurement of the left ventricular minor axis at the level of the papillary muscles [10]. The echocardiograph is equipped with mechanisms for frame by frame analysis and with electronic calipers for measuring end diastolic and end systolic minor axis diameters, both in the long and short axis views and an average of five measurements of each was obtained. End diastolic diameter (EDD) was measured at the beginning of the R-wave of the cardiac cycle and end systolic diameter (ESD) at the smallest dimension observed of the same cardiac cycle. Left ventricular ejection time (LVET) was measured from M-mode paper recording of the aortic valve motion. Left ventricular function was assessed by calculating changes in EDD, ESD,

ejection fraction: EF = (EDV − ESV)/EDV × 100%, EDV and ESV calculated according to Teichholz et al [11]; percentage fractional shortening of the minor diameter: FS = (EDD − ESD)/EDD × 100%, and mean velocity of circumferential fiber shortening: VCF = (EDD − ESD)/(EDD × LVET) circ/sec.

Impedance cardiography. Stroke volume (SV), heart rate (HR) and cardiac output (CO) were measured by Impedance Cardiograph (model 304A, Surcom Inc., U.S.A.). This non-invasive technique has been evaluated in our laboratory and found to be accurate and reliable, with a random error of less than five percent [12, 13]. Briefly, this consisted of utilizing four bands of mylar–backed self–adhesive aluminum electrodes, two of which were placed around the neck at least 3 cm apart, the third at the level of the xiphisternum and the fourth at the level of the umbilicus. A constant sinusoidal alternating current of 4 ma RMS and 100 KHz was passed through the thorax, between the outer electrodes. The average total impedance (Z_0, ohm), rate of change of impedance (dz/dt, ohm/sec) and LVET (sec) through each cardiac cycle, together with simultaneous electrocardiogram and phonocardiogram were obtained while the patient remained motionless and with the breath held at normal end-expiration. SV (ml/beat) was calculated from,

$$SV = (P \times L^2 \times dZ/dt_{min} \times LVET)/Z_0^2$$

where P is resistivity of blood ($P = 53.2e^{0.022H}$), H is hematocrit (%) obtained from blood samples drawn each time recordings were made, L is average distance (cm) between the inner pair of electrodes measured at the midline, anteriorly and posteriorly, dZ/dt_{min} = minimum rate of change of impedance occurring during the cardiac cycle (ohm/sec). The SV at each measurement was calculated from an average of five cardiac cycles. CO was derived from the product of HR and SV of these cardiac cycles.

Measurement of blood pressure. In order to avoid intra- and interobserver variations, blood pressure was measured following each impedance cardiography recording using an automatic blood pressure measuring device (Infrasonde D4000, Puritan Bennet Corporation, USA). Mean arterial pressure (MAP) was calculated as diastolic plus one–third pulse pressure. Systemic vascular resistance (SVR) was estimated from the formula: (80 × MAP)/CO where the CO was obtained from the impedance cardiograms recorded at the same time.

Biochemistry

Blood was drawn for biochemical and gas analysis just before and after a treatment run. Blood urea nitrogen, plasma creatinine, calcium, protein, albumin, glucose, sodium, potassium and chloride were determined with routine automated methods; plasma osmolality was measured using the freezing point depression method. Blood gases were analyzed with a Corning 178 gas analyzer.

Experimental protocol

The assessment of cardiac function was performed just before, during and immediately after a treatment run. Each patient underwent two assessments, once during the four months of the H HDF treatment and once during the four months of the HD treatment. A period of "stabilization" on each procedure was allowed and studies were conducted 59 ± 12 days after the start of H HDF and 64 ± 12 days after the start of HD, respectively. In addition to pre- and post-treatment measurements, echocardiography was performed three times, and impedance cardiography and blood pressure measurements six times at equal time intervals during the treatment run. During a three hour run, echocardiography was done every 60 minutes and impedance cardiography and blood pressure measurements made every 30 minutes. These intervals were increased to 80 minutes and 40 minutes, respectively, during a four hour run. This allowed the comparability of results despite the different treatment times.

Echocardiograms and impedance cardiograms were analyzed without knowledge of which type of dialysis treatment was under study.

Statistical analysis

A factorial analysis was employed for purposes of comparing multiple measurements, that is, echocardiography and impedance cardiography results, during a treatment run and comparing the two treatment modalities. Where the results of the factorial analysis were significant, the difference between means was detected by a Least Significant Difference test [14]. A paired Student's *t*-test was used in the case of biochemical and gas analysis where only pre- and post-treatment measurements were made. In both instances a $P < 0.05$ was accepted as statistically significant. Results were expressed as means ± SEM.

Results

The 10 patients completed four months each with HD and H HDF without experiencing hypotension. Treatment sessions were three times per week. At each treatment session, the duration for treatment was decided by the attending nephrologist. Over each of the four month periods, treatment duration for H HDF ranged from 180 to 240 minutes, with a mean of 206 ± 9 minutes; and for HD it ranged from 240 to 360 minutes with a mean of 285 ± 14 minutes. Besides the blood biochemistry evaluation as performed for this study, monthly measurements of blood biochemistry to monitor the patients' nutritional status were done. In each case blood was taken before the midweek treatment run for this purpose. Consecutive monthly plasma albumin levels while the patients were on H HDF were 42.9 ± 1.6 g/liter, 41.2 ± 0.9 g/liter, 42.7 ± 0.9 g/liter and 42.3 ± 1.1 g/liter, and while on HD they were 42.9 ± 1.2 g/liter, 43.8 ± 1.2 g/liter, 43.3 ± 1.4 g/liter and 42.1 ± 0.8 g/liter. The corresponding hematocrit levels were 27.0 ± 1.1%, 26.9 ± 1.4%, 27.4 ± 1.3% and 26.1 ± 0.9% for H HDF, and 26.2 ± 1.0%, 27.3 ± 1.1%, 27.1 ± 1.1% and 26.7 ± 1.5% for HD. Plasma transferrin levels for H HDF during the first, second and fourth month were 2.6 ± 0.2 g/liter, 2.6 ± 0.2 g/liter and 2.5 ± 0.1 g/liter, respectively; for HD, they were 2.4 ± 0.2 g/liter, 2.6 ± 0.1 g/liter and 2.4 ± 0.1 g/liter. No significant inter- or intra-treatment differences were found in the plasma albumin, transferrin and hematocrit. During the four month treatment periods mean blood urea nitrogen before the treatment runs was 29.1 ± 0.7 mmol/liter for H HDF and 29.2 ± 0.6 mmol/liter for HD. The corresponding plasma creatinine levels were 1283 ± 26 μmol/liter for H HDF and 1265 ± 13 μmol/liter for HD. There were no significant intra-treatment differences in these levels of blood urea nitrogen or plasma creatinine.

Echocardiography

In the pre-treatment phase, there was no significant different in ESD and EDD between the two methods of treatment. During and immediately after treatment with H HDF (when the blood in the dialyzing system had been returned to the patient), a significant decrease in ESD was noted. The last three of the total of five measurements were significantly lower than the initial two ($P < 0.05$). Also, these three values were significantly lower than those obtained in patients on HD ($P < 0.05$). With HD, there was a gradual decrease in ESD also but this change was not statistically significant (Fig. 1A).

There was a trend towards a smaller EDD with both H HDF and HD but no statistically significant differences could be demonstrated between the two methods or during sessions on each type of treatment (Fig. 1B).

No significant difference in LVET was found between the patients on the two methods of treatment before the session. LVET decreased gradually as treatment proceeded and the trend towards a shorter ejection time was more obvious with H HDF than with HD (Fig. 1C). These differences were not significant.

In the pre-treatment phase, the mean VCF was not significantly different in patients treated by the two methods. However, a significant increase in mean VCF was found with H HDF during the session, the last three of the five measurements being consistently higher than the first two ($P < 0.05$). These values were higher than the corresponding values when the patients were on HD ($P < 0.05$). With HD there was a similar trend but only the measurement at the end of treatment was significantly higher than the others ($P < 0.05$) (Fig. 1D).

Both EF and FS were significantly higher when the patients were on H HDF than when they were on HD before a treatment session and this difference was maintained during and after completion of the session (both $P < 0.05$). No significant trends were seen in either EF or FS during the two sessions on the two methods (Fig. 1, E and F).

Impedance cardiography

HR, SV and CO before treatment were similar when the patients were on either H HDF or HD. During treatment with either method, there was a trend towards a smaller SV and higher HR, but none attained statistical significance (Fig. 2A and B). With H HDF, there was a tendency towards a greater SV and a slower HR when compared with HD but no statistical significance could be demonstrated. CO remained unchanged (Fig. 2C). On completion of treatment, after the blood in the dialysis system has been returned to the patients, there was a sudden increase in SV, (tending to return the SV to pre-treatment levels) associated with a decrease in HR and an increase in CO. This increase in SV was again more obvious with H HDF than with HD but did not attain statistical significance.

A small, inconsistent and statistically insignificant decrease in MAP was noted during treatment (Fig. 3A). Similarly, an inconsistent trend towards a reduced SVR was found (Fig. 3B).

Tables 2 and 3 summarize the results of the echocardiography and impedance cardiography measurements.

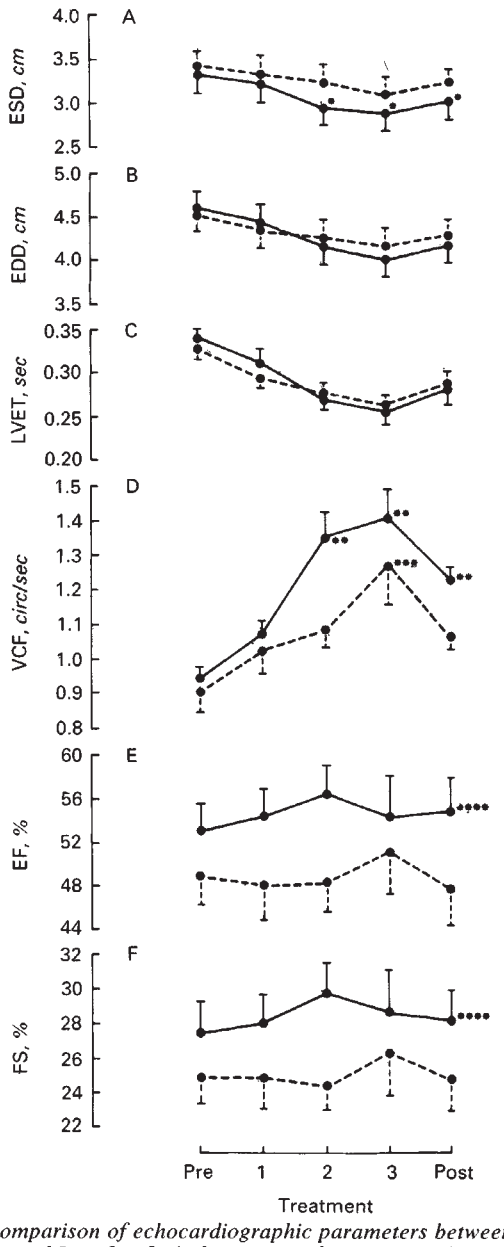

Fig. 1. *Comparison of echocardiographic parameters between H HDF (●——●) and HD (●---●) before (Pre), after (Post) and 3 times during treatment at equal time intervals.* Abbreviations are: ESD, end systolic diameter; EDD, end diastolic diameter; LVET, left ventricular ejection time; VCF, mean velocity of circumferential shortening; EF, ejection fraction; FS, fractional shortening. (*) in A indicates that the last 3 measurements of ESD with H HDF were significantly lower ($P < 0.05$) than the initial 2, and all 5 measurements with HD. (**) in D shows that the last 3 mean VCF were significantly greater ($P < 0.05$) than the initial 2 with H HDF and the corresponding measurements when patients were on HD. (***) in D indicates that this mean VCF was significantly greater ($P < 0.05$) than the other 4 measurements with HD. (****) in E and F shows that EF and FS during H HDF were significantly greater ($P < 0.05$) than with HD before treatment, and this difference was maintained throughout the treatment run, with no intra-treatment differences found with either H HDF or HD. All values are expressed as means ± SEM. Comparisons were made using a factorial analysis.

Biochemistry

Plasma calcium and bicarbonate at the start of the treatment runs were higher in H HDF than in HD. This difference was

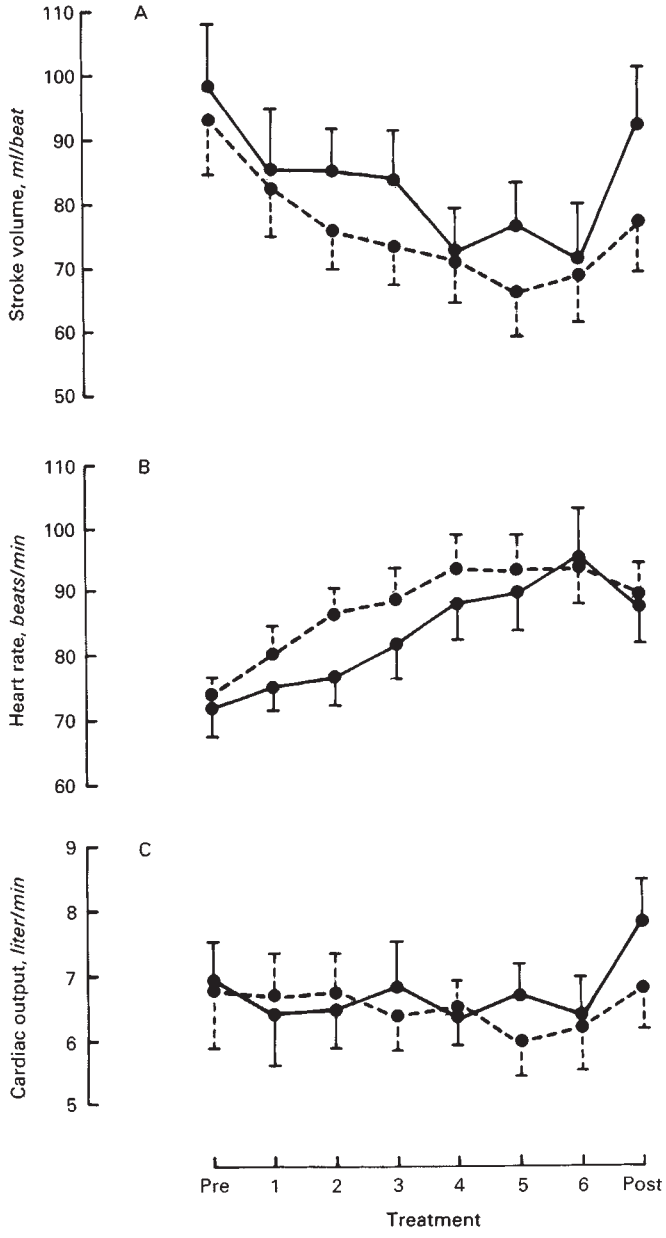

Fig. 2. *Comparison of stroke volume, heart rate and cardiac output between H HDF (●——●) and HD (●---●) before (Pre), after (Post) and 6 times during treatment at equal time intervals.* No significant intra and inter-treatment differences were found, using a factorial analysis. All values are expressed as means ± SEM.

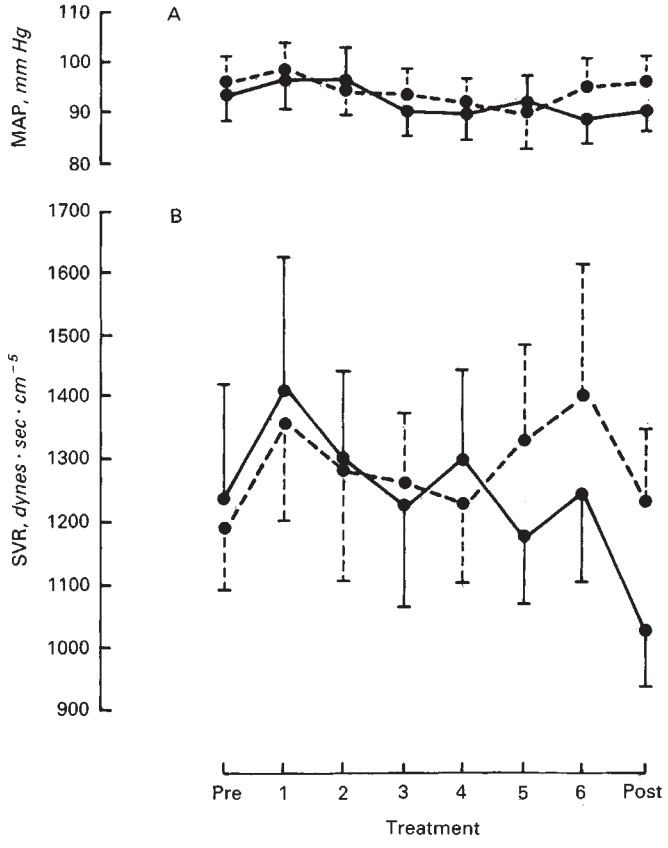

Fig. 3. *Comparison of mean arterial pressure (MAP) and systemic vascular resistance (SVR) between H HDF (●——●) and HD (●---●) before (Pre), after (Post) and 6 times during treatment at equal time intervals.* No significant intra and inter-treatment differences were found using a factorial analysis. All values are expressed as means ± SEM.

enhanced at the end of the run. Further, plasma glucose, sodium, osmolality and $PaCO_2$ at the end of the run were significantly higher in H HDF than in HD (Table 4).

Discussion

Study design

This study was undertaken to evaluate the 'acute' and 'chronic' effects of H HDF on cardiac function in a group of relatively young patients without evidence of coronary heart disease, heart failure or pericardial effusion. Patients were studied approximately two months after they had started on H HDF or HD to allow for stabilization with the assigned method. Any changes observed between groups in the pre-treatment phase of each session were designated chronic effects. Examinations were also carried out during the treatment session to obtain a profile of acute changes in cardiac function. This design differed from those of previous studies relating to cardiac function during dialysis in several important aspects [5, 6, 15–18].

Cardiac function was assessed sequentially during an entire session. All the assessments were done noninvasively [19], and finally, a two-month stabilization period was used in this study to permit equilibration of the patients. Impedance cardiography was used to assess SV and CO as it was felt that this technique offered greater accuracy and reproducibility of the results, as previously reported from this laboratory [12, 13]. Due to the different treatment times in HD and H HDF and to allow for comparability of the results, an equal number of measurements at equal intervals during dialysis were made, the duration of the intervals being dependent on the actual dialysis time required for each patient. Assuming that the rate of fluid loss was more or less constant during either procedure, comparisons could be

Table 2. Cardiovascular data derived from echocardiography in ten patients before, during and after a run of hypertonic hemodiafiltration (H HDF) and a run of hemodialysis (HD)

Normal range	ESD *cm* 2.0–3.4	EDD *cm* 3.7–5.6	LVET *sec*[a]	VCF *circ/sec* 1.02–1.94	EF %[e] 55–84	FS %[e] 25–42
Pre-treatment						
H HDF	3.33 ± 0.21	4.58 ± 0.23	0.290 ± 0.012	0.943 ± 0.035	53.1 ± 2.8	27.5 ± 1.8
HD	3.41 ± 0.20	4.52 ± 0.21	0.277 ± 0.011	0.904 ± 0.054	48.9 ± 2.7	24.9 ± 1.6
During treatment						
#1 H HDF	3.22 ± 0.22	4.44 ± 0.23	0.263 ± 0.015	1.072 ± 0.044	54.4 ± 2.6	28.1 ± 1.7
HD	3.33 ± 0.23	4.34 ± 0.21	0.244 ± 0.011	1.025 ± 0.070	48.1 ± 3.5	24.9 ± 1.8
#2 H HDF	2.95 ± 0.21[b]	4.18 ± 0.24	0.221 ± 0.019	1.355 ± 0.070[c]	56.6 ± 2.5	29.7 ± 1.8
HD	3.23 ± 0.22	4.25 ± 0.23	0.226 ± 0.010	1.083 ± 0.051	48.3 ± 2.7	24.4 ± 1.4
#3 H HDF	2.88 ± 0.23[b]	4.01 ± 0.22	0.208 ± 0.019	1.407 ± 0.085[c]	54.4 ± 3.1	28.7 ± 2.5
HD	3.08 ± 0.21	4.16 ± 0.21	0.211 ± 0.013	1.272 ± 0.117[d]	51.1 ± 3.4	26.3 ± 2.4
Post-treatment						
H HDF	3.00 ± 0.20[b]	4.17 ± 0.22	0.229 ± 0.017	1.226 ± 0.044[c]	54.9 ± 3.1	28.2 ± 1.7
HD	3.22 ± 0.17	4.28 ± 0.19	0.236 ± 0.013	1.06 ± 0.335	47.7 ± 3.4	24.8 ± 1.9

[a] Varies inversely with heart rate
[b] Significantly < initial 2 measurements with H HDF and all 5 with HD ($P < 0.05$)
[c] Significantly > initial 2 measurements with H HDF and the corresponding measurements with HD ($P < 0.05$)
[d] Significantly > the other 4 measurements during HD ($P < 0.05$)
[e] EF and FS with H HDF > with HD before, during and after the treatment run ($P < 0.05$)

Table 3. Cardiovascular data derived from impedance cardiography in ten patients before, during and after a run of hypertonic hemodiafiltration (H HDF) and a run of hemodialysis (HD)

	HR *beats/min*	SV *ml/beat*	CO *liter/min*	MAP *mm Hg*	SVR *dynes · sec · cm*$^{-5}$
Pre-treatment					
H HDF	71.8 ± 4.4	98.2 ± 9.6	6.91 ± 0.68	94.4 ± 6.7	1238 ± 186
HD	73.7 ± 3.4	93.1 ± 8.3	6.79 ± 0.88	94.7 ± 6.1	1190 ± 100
During treatment					
#1 H HDF	75.3 ± 3.8	85.3 ± 9.2	6.43 ± 0.79	97.5 ± 6.8	1412 ± 215
HD	80.1 ± 4.5	82.4 ± 7.9	6.63 ± 0.80	98.5 ± 5.6	1361 ± 162
#2 H HDF	76.4 ± 4.3	85.1 ± 6.4	6.49 ± 0.60	96.5 ± 6.2	1302 ± 144
HD	86.6 ± 4.0	75.5 ± 6.4	6.73 ± 0.66	94.7 ± 5.5	1280 ± 177
#3 H HDF	81.6 ± 5.5	83.8 ± 7.3	6.82 ± 0.76	90.7 ± 5.2	1225 ± 167
HD	88.6 ± 5.0	73.1 ± 6.2	6.35 ± 0.50	93.5 ± 5.7	1262 ± 117
#4 H HDF	88.0 ± 5.6	72.2 ± 6.6	6.39 ± 0.77	90.8 ± 6.0	1298 ± 147
HD	93.5 ± 6.2	71.0 ± 7.0	6.41 ± 0.51	91.0 ± 6.1	1228 ± 132
#5 H HDF	89.8 ± 6.4	76.2 ± 6.9	6.64 ± 0.55	91.3 ± 6.1	1177 ± 112
HD	93.1 ± 5.8	65.5 ± 7.0	5.92 ± 0.55	90.3 ± 7.4	1333 ± 158
#6 H HDF	94.9 ± 7.6	70.6 ± 8.3	6.36 ± 0.58	89.5 ± 5.6	1247 ± 150
HD	94.0 ± 6.2	68.2 ± 7.2	6.18 ± 0.69	95.3 ± 5.5	1404 ± 203
Post-treatment					
H HDF	87.7 ± 6.0	91.7 ± 8.9	7.80 ± 0.68	90.7 ± 3.8	1023 ± 94
HD	89.4 ± 4.6	76.5 ± 7.9	6.79 ± 0.62	96.3 ± 5.9	1230 ± 119

Note: For each parameter, no inter- or intratreatment differences were found.

made at each interval point despite the different treatment times.

Ventricular function

The changes in ventricular function with both HD and H HDF were similar to earlier studies with HD in that there was a decrease in EDD, ESD and LVET and an increase in mean VCF [5, 6, 15]. The finding that EF and FS did not change significantly was also noted previously [18]. Contrary to some reports [5, 6] a significant decrease in EDD was not found during HD in this study. However, this apparent discrepancy could have arisen because of the type of statistical analysis employed. In the earlier reports [5, 15], measurements were made before and after a treatment session, and the authors rightly used a paired *t*-test to compare the results. In the present study, since multiple observations involving two forms of treatment were made, a factorial analysis incorporating an analysis of variance was thought to be a more appropriate test of statistical significance. Indeed, if one were to compare only the observations made before and after the treatment session using a paired *t*-test, a highly significant decrease in EDD could be demonstrated in both HD ($P < 0.025$) and H HDF ($P <$

Table 4. Biochemical data in ten patients before and after a run of hypertonic hemodiafiltration (H HDF) and a run of hemodialysis (HD)

	PRE		POST	
	H HDF	HD	H HDF	HD
Blood urea nitrogen *mmol/liter*	29.1 ± 2.7	29.9 ± 2.5	12.3 ± 1.5	12.5 ± 1.5
Plasma creatinine *μmol/liter*	1340 ± 78	1326 ± 87	628 ± 51	646 ± 64
Plasma calcium *mmol/liter*	2.28 ± 0.05[a]	2.21 ± 0.04	2.99 ± 0.05[c]	2.70 ± 0.08
Plasma protein *g/liter*	65.9 ± 0.9	65.7 ± 1.4	81.8 ± 2.1	79.7 ± 3.5
Plasma albumin *g/liter*	39.9 ± 1.0	39.7 ± 1.3	50.2 ± 1.4	48.9 ± 2.2
Plasma glucose *mmol/liter*	5.2 ± 0.4	6.1 ± 0.5	7.3 ± 0.4[c]	5.5 ± 0.4
Plasma sodium *mmol/liter*	139.7 ± 0.7	138.4 ± 0.3	140.8 ± 1.0[b]	136.9 ± 1.0
Plasma potassium *mmol/liter*	5.5 ± 0.4	5.1 ± 0.3	3.0 ± 0.1	3.2 ± 0.2
Plasma chloride *mmol/liter*	103.4 ± 0.8	104.7 ± 0.6	101.0 ± 0.7	101.8 ± 0.5
Plasma osmolality *mmol/kg H_2O*	312.6 ± 2.8	313.0 ± 2.8	298.4 ± 2.7[b]	288.3 ± 3.8
Arterial PO_2 *mm Hg*	87.5 ± 4.2	91.4 ± 2.9	82.2 ± 2.1	89.3 ± 4.6
Arterial PCO_2 *mm Hg*	35.2 ± 1.5	32.0 ± 1.2	32.5 ± 1.3[b]	28.5 ± 1.0
Arterial $[H^+]$ *nmol/liter*	40.5 ± 0.6	44.1 ± 1.9	33.8 ± 0.8	35.5 ± 0.9
Arterial bicarbonate *mmol/liter*	20.9 ± 0.9[a]	17.6 ± 0.7	23.1 ± 0.9[b]	19.3 ± 0.7

All values are expressed as means ± SEM.
[a] $P < 0.03$; [b] $P < 0.01$; [c] $P < 0.001$, Students's paired *t*-test

0.005) in the present study. The same could also be demonstrated for LVET in both HD ($P < 0.005$) and H HDF ($P < 0.001$) as well as for SV (both, $P < 0.05$).

A number of distinct features associated with H HDF as compared to HD are emphasized. While there was a similar trend towards a smaller EDD and shorter LVET as treatment proceeded with both H HDF and HD, ESD became significantly smaller only when the patients were on H HDF. This significant decrease in ESD was reflected in an enhancement of the increase in mean VCF, especially during the second half of the treatment session. The increase in VCF found in the patients while on HD was similar to that reported by others [5, 6, 15, 16]. However, at corresponding points of assessment during treatment, the VCF was higher with H HDF than with HD and this difference reached statistical significance in the last three measurements. These findings suggest that while acute improvements in left ventricular function occurred with both forms of treatments, H HDF was associated with a bigger improvement.

Further, it has been suggested that decreases in end systolic parameters such as end systolic volume are sensitive indicators of myocardial function, especially in the absence of significant changes in cardiac pre-load, afterload or heart rate [20]. It may therefore be suggested that the significant decreases in ESD noted in this study offers a further indication that H HDF was associated with a greater acute improvement in ventricular function during the treatment run.

There were significant increases in EF and FS in the pre-treatment phase of each session when the patients were on H HDF than when they were on HD. These differences were observed before any changes in pre-load and afterload that may have occurred during the sessions. Also, these differences were maintained during the treatment runs with no significant intra-treatment differences during either H HDF or HD. Such a finding could suggest a chronic effect due to the treatment modality, particularly as the patients had undergone an average of two months of either H HDF or HD before the study was made.

It is of interest to note the apparent discrepancy between these changes in EF and FS and the changes noted with ESD and VCF. These findings have some features in common with the report by Chaignon et al [18] who showed that there were no significant alterations in EF and FS during dialysis, but VCF increased significantly in patients so treated. It is generally accepted that EF, FS and VCF reflect the basal contractile state of the ventricle [21]. During dialysis, there are shifts in fluid volume and simultaneous changes in pre-load and afterload. It has been suggested that these indices may be affected secondarily by such changes and that the differences observed are not indicative of changes in contractility per se [22, 23]. However, Ross [24] concluded that when both pre-load and afterload were simultaneously increased or decreased, mean VCF remained nearly constant. Indeed, Chaignon et al suggested that mean VCF might be more sensitive than EF as an index to follow changes in cardiac function during dialysis [18].

In the present study, MAP and SVR, reflecting afterload, did not change significantly during treatment with both methods. There was no difference also between the forms of treatment. EDD, which reflects pre-load [25], decreased during both treatments, though not significantly. With H HDF, as compared with HD, there was a significant decrease in ESD and a greater (but not significant) decrease in LVET. The combination of these two factors contributed to a greater change in mean VCF with H HDF. With EF and FS, which are not related to LVET, such differences were not evident. These considerations could explain why EF and FS did not change significantly during a treatment run in this study or in that of Chaignon et al [18]. LVET has been shown to vary inversely with heart rate [26]. In this study, a trend towards a shorter LVET with H HDF was noted despite a slower heart rate at each point of assessment. It is suggested that this change reflects an improvement in ventricular function also.

The CO did not change significantly during treatment with either H HDF or HD. These findings are comparable to those reported by Mansell et al [27] who compared intra-dialysis changes of CO in patients with high or normal blood acetate levels. They observed also that in the group of patients with steady acetate levels during HD, there was a gradual but not significant decrease in CO, which then returned to near pre-dialysis level on completion of dialysis following return of the

blood contained in the dialyzer to the patient. In the present study it was found that the changes in CO were due mainly to the gradual decrease in SV and that this change was compensated partially by a gradual rise in HR.

There was a modest trend towards a greater SV and slower HR with H HDF when compared with HD, though this change was not significant. During treatment with either method, there was a gradual but statistically insignificant drop in SV and increase in HR. Leenen et al [17] also found the same trend during HD. Significant decreases in SV accompanied by hypotension were noted by Mansell et al [27]. A significant decrease in MAP was not found in the present study probably due to the absence of a significant reduction in SV during treatment.

In summary, the results of the present study are consistent with the findings that improved myocardial contractility was the major contributing factor in the improved cardiac function associated with H HDF.

Equivalence of HD and H HDF treatments

It is possible that the differences in ventricular function that were found could be due to differences in the solute transport characteristics of these two different treatment methods. Kinetic modelling of small molecules (urea, creatinine) was not used to define adequacy or equivalence of these treatment methods. The pre-treatment levels of urea and creatinine were similar. In the "long term" studies which involved a four–month treatment period, the following nutritional parameters were also similar: albumin, transferrin and hematocrit. In addition, the routine clinical assessment of these patients found them to be adequately dialyzed and nutritionally unchanged. It was concluded, because of the above considerations, that these treatment methods were comparable and that the differences in ventricular function were not due to a more adequate treatment provided by H HDF.

Biochemical factors

Significant increases in plasma calcium and bicarbonate were found when the patients were on H HDF before a treatment session and these differences were enhanced at the end of the run when compared with the results when the patients were on HD. There is some evidence to suggest that these findings may have a role to play in the improvement of cardiac function with H HDF.

Chaignon et al [18] postulated that an improvement in left ventricular function may be due to an increase in intra-dialytic serum calcium and a concomitant decrease in serum potassium concentration. Similar results were reported by Henrich, Hunt and Nixon [28] who showed a positive correlation between increasing intra-dialytic plasma, ionized calcium levels and improved left ventricular function. It is of interest to note that pre-treatment plasma calcium levels were significantly higher when our patients were on H HDF than when they were on HD, due to a more positive calcium balance. Further, while calcium levels were increased following dialysis with both methods, the difference in calcium concentration between the two treatment modalities was at a higher level of significance. This difference may explain the greater improvement in left ventricular function associated with H HDF, both over the long and the short term. However, the mechanism for this improvement remains unclear and needs further evaluation. For example, the role of calcium may be studied using different calcium concentrations in dialysates in experiments similar to the present study.

Experimental studies have shown that metabolic acidosis can decrease cardiac contractility [29, 30]. Smith et al [31] pointed out, however, that the depressive effects of metabolic acidosis were considerably less than suspected. Furthermore, the increase in plasma bicarbonate levels during dialysis did not improve ventricular contractility in the study by Henrich et al [28]. Thus, the evidence for increased levels of plasma bicarbonate, as found in this study, as a factor for the improved cardiac function appears less clear.

In summary, this study shows that H HDF, compared with HD, is associated with a better myocardial function, both in the short and long term. There is some evidence that plasma calcium levels may play a role in causing this improvement. Other factors, for example a significantly higher plasma osmolality, was noted in this study to be associated with H HDF. This change in osmolality could be involved in preserving the plasma volume more efficiently during treatment with H HDF and indirectly influencing ventricular function, and it is suggested that additional studies are needed to investigate this aspect. It is suggested also that during treatment with H HDF further experiments should be performed to examine the effects of H HDF on ventricular function in protocols where patients are treated without a change in weight. Finally, the improvement in ventricular function may be due to the more efficient removal by H HDF of an as yet unidentified myocardial toxin [32].

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References

1. Leber HW, Wizemann V, Goubeaud G, Rawer P, Schutterle G: Simultaneous hemofiltration/hemodialysis: An effective alternative to hemofiltration and conventional hemodialysis in the treatment of uremic patients. *Clin Nephrol* 9:115–121, 1978
2. Basile C, Granger A, Scatizzi A: Sodium kinetics in hypertonic hemodiafiltration, in *Progress in Artificial Organs-1983*, edited by Atsumi K, Maekawa M, Ota K, Cleveland, ISAO Press No. 204, 1984, p. 575
3. Basile C, Di Maggio A, Curino E, Scatizzi A: Pharmacokinetics of netilmicin in hypertonic hemodiafiltration and standard hemodialysis. *Clin Nephrol* 24:305–309, 1985
4. Basile C, Di Maggio A, Scatizzi A: Long–term experience with hypertonic hemodiafiltration. *Proc Eur Dial Transplant Assoc* 22:303–307, 1985
5. Gilmartin JJ, Duffy BS, Finnegan P, McCready N: Non invasive study of left ventricular function in chronic renal failure before and after hemodialysis. *Clin Nephrol* 20:55–60, 1983
6. Nixon JV, Mitchell JH, McPhaul JJ Jr, Henrich WL: Effect of hemodialysis on left ventricular function. Dissociation of changes in filling volume and in contractile state. *J Clin Invest*

71:377–384, 1983
7. BASILE C, DI MAGGIO A, LONGO S, SCATIZZI A: Sodium balance in hypertonic hemodiafiltration. *Blood Purification* 2:70–75, 1984
8. KIRKWOOD RG, O'BRIEN M, BUTRUILLE Y, LAZARUS JM, GOTTLIEB MN, LOWRIE EG: Initial clinical evaluation of the Hospal artificial kidney system. *Trans Am Soc Artif Intern Organs* 24:509–515, 1978
9. BASILE C, DI MAGGIO A, MANENTE G, GUGLIOTTA F, SCATIZZI A: Solute kinetics in hypertonic hemodiafiltration and standard hemodialysis. *Am J Kidney Dis* 7:483–489, 1986
10. FEIGENBAUM H: *Echocardiography* (3rd ed). Philadelphia, Lea and Febiger, 1981, p. 149.
11. TEICHHOLZ LE, KREULEN T, HERMAN MV, GORLIN R: Problems in echocardiographic volume determinations: Echocardiographic–angiographic correlations in the presence and absence of synergy. *Am J Cardiol* 37:7–11, 1976
12. TEO KK, HETHERINGTON MD, HAENNEL RG, GREENWOOD PV, ROSSALL RE, KAPPAGODA T: Cardiac output measured by impedance cardiography during maximal exercise tests. *Cardiovascular Res* 19:737–743, 1985
13. HETHERINGTON M, TEO KK, HAENNEL R, GREENWOOD P, ROSSALL RE, KAPPAGODA T: Use of impedance cardiography in evaluating the exercise response of patients with left ventricular dysfunction. *Eur Heart J* 6:1016–1024, 1985
14. SNEDECOR GW, COCHRAN WG: *Statistical methods* (7th ed). Ames, Iowa State University Press, 1980, p. 233, 318, 325
15. MEHTA BR, FISCHER D, AHMAD M, DUBOSE TD JR: Effects of acetate and bicarbonate hemodialysis on cardiac function in chronic dialysis patients. *Kidney Int* 24:782–787, 1983
16. SHICK EC JR, IDELSON BA, LIANG C, REDLINE RC, BERNARD DB: Comparison of the hemodynamic response to hemodialysis with acetate or bicarbonate. *Trans Am Soc Artif Intern Organs* 29:25–28, 1983
17. LEENEN FHH, BUDA AJ, SMITH DL, FARREL S, LEVINE DZ, ULDALL PR: Hemodynamic changes during acetate and bicarbonate hemodialysis. *Artif Organs* 8:411–417, 1984
18. CHAIGNON M, CHEN WT, TARAZI RC, NAKAMOTO S, SALCEDO E: Acute effects of hemodialysis on echographic–determined cardiac performance: Improved contractility resulting from serum increased calcium with reduced potassium despite hypovolemic–reduced cardiac output. *Am Heart J* 103:374–378, 1982
19. KINET JP, SOYEUR D, BALLAND N, SAINT–REMY M, COLLIGNON P, GODON JP: Hemodynamic study of hypotension during hemodialysis. *Kidney Int* 21:868–876, 1982
20. MITCHELL JH, WILDENTHAL K: Problems in measurement of myocardial contractility. *Proc Roy Soc Med* 65:542–545, 1972
21. BRAUNWALD E: *Heart disease* (2nd ed). Philadelphia, WB Saunders Co, 1984, p. 480
22. HIRSHLEIFER J, CRAWFORD M, O'ROURKE RA, KARLINER JS: Influence of acute alterations in heart rate and systemic arterial pressure on echocardiographic measures of left ventricular performance in normal human subjects. *Circulation* 52:835–841, 1975
23. NIXON JV, MURRAY RG, LEONARD PD, MITCHELL JH, BLOMQVIST CG: Effect of large variations in preload on left ventricular performance characteristics in normal subjects. *Circulation* 65:698–703, 1982
24. ROSS J JR: Afterload mismatch and preload reserve: A conceptual framework for the analysis of ventricular function. *Prog Cardiovas Dis* 18:255–264, 1976
25. BRAUNWALD E: *Heart disease* (2nd ed). Philadelphia, WB Saunders Co. 1984, p. 433
26. WEISSLER AM, PEELER RG, ROCHEL WH: Relationships between left ventricular ejection time, stroke volume, and heart rate in normal individuals and patients with cardiovascular disease. *Am Heart J* 62:367–378, 1961
27. MANSELL MA, CROWTHER A, LAKER MF, WING AJ: The effect of hyperacetatemia on cardiac output during regular hemodialysis. *Clin Nephrol* 18:130–134, 1982
28. HENRICH WL, HUNT JM, NIXON JV: Increased ionized calcium and left ventricular contractility during hemodialysis. *N Eng J Med* 310:19–23, 1984
29. WANG H, KATZ RL: Effects of changes in coronary blood pH on the heart. *Circ Res* 17:114–122, 1965
30. NG ML, LEVY MN, ZIESKE HA: Effects of changes of pH and of carbon dioxide tension on left ventricular performance. *Am J Physiol* 213:115–120, 1967
31. SMITH NT, CORBASCIO AN: Myocardial resistance to metabolic acidosis. *Arch Surgery* 92:892–897, 1966
32. RAAB W, BURLINGTON V: Cardiotoxic substances in the blood and heart muscle in uremia (their nature and action). *J Lab Clin Med* 29:715–734, 1944